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EXAMINER	
CORDERO GARCIA, MARCELA M	
ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/599,976	SCHELLER ET AL.	
	Examiner	Art Unit	
	MARCELA M. CORDERO GARCIA	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 July 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,14,16-18,20 and 24-52* is/are pending in the application.

4a) Of the above claim(s) *37-39,50 and 51* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,14,16-18,20 and 24-36, 40-49, 52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/9/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This Office Action is in response to the reply received on July 9, 2010.

Any rejection from the previous office action, which is not restated here, is withdrawn.

Election/Restrictions

2. Applicant's election without traverse of the species SPM-927, drawn to a compound of the formula IIb wherein Ar is unsubstituted phenyl, R3 is methoxymethyl, R1 is methyl and CSD associated condition is "chronic headache" in the reply filed on December 4, 2009 is acknowledged. The claims were generically examined with respect to formula IIb.

Status of the claims

3. Claims 1-4, 14, 16-18, 20, 24-52 were pending in the application. Claims 37-39 and 50-51 are withdrawn. Claims 1-4, 14, 16-18, 20, 24-36, 40-49 and 52 are readable upon the elected species/group and are therefore presented for examination on the merits. Please note that claim 40 was previously added to Group II, but it should have been in Group I, so it is now being examined.

Amendment of the title

4. Preliminary Amendment (Amendment A) filed 16 October 2006, wherein Applicant requested amendment of the title to METHODS FOR PROPHYLAXIS OR TREATMENT OF CONDITIONS ASSOCIATED WITH CORTICAL SPREADING DEPRESSION has been entered. A new bibliographic data sheet has been herein attached with the title change.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

6. Claims 1-4, 14, 16-18, 20, 24, 32-36, 41, 44, 46-47 are rejected under 35 U.S.C. 102(b) as being anticipated by Harris (US 2002/0086828) and under 35 U.S.C. 102(e) as being anticipated by Harris (US 6,884,910, cited in the IDS dated 12/4/2009).

Harris (US 2002/0086828) is the patent application corresponding to Harris (US 6,884,910). For the sake of clarity the rejection refers to Harris US 2002/0086828. However, it is noted that Harris US 6,884,910 contains parallel teachings.

Harris discloses a method of treating chronic headaches, migraines and acute migraines with the compound (R)-2-acetamido-N-benzyl-3-methoxypropionamide and

also with other compounds embraced by the genus of Formula II, i.e., O-methyl-N-acetyl-D-serine-p-fluorobenzylamide, O-methyl-N-acetyl-D-serine-p-fluorobenzyl amide, etc. (e.g., pages 7-8).

Harris teaches that a migraine headache is defined as a periodically occurring (i.e., chronic) vascular headache characterized by pain in the head (usually unilateral), nausea and vomiting, photophobia, phenophobia, vertigo and general weakness. Migraine is the most common type of vascular headache and affects as amny as 15% of the world's population. Of the different types of migraines, classical migraine and common migraine are the two most prevalent. The major difference between the two types of migraines is that classical migraines are preceded by the appearance of neurological symptoms before an attack whereas common migraines are not preceded by such symptoms. Migraine is caused by intermittent brain dysfunction. However, the precise pathophysiological mechanism involved are not understood. The head-pain is believed to involve blood vessel dilation and a reduction of the brain's pain relieving chemicals. Harris teaches that analgesics are often used to treat infrequent and mild migraines. Analgesics reduce the pain of a migraine in the case of aspirin also discourage clumping of blood platelets. However, for moderate to severe migraines, stronger medication is necessary, e.g., ergotamine, or 5-H-T1 agonists like sumatriptan (page 1). Harris goes on to teach that alternatives for treatment are necessary given the inadequacy of current therapy in completely alleviating the pain from those who have moderate to heavy (i.e., acute) migraine headaches (page 1).Harris discloses that a migraine headache is a paroxysmal disorder characterized by recurrent attacks of

headaches, which may be associated with visual (as in cluster type headaches) or GI disturbances, the pain is usually generalized, but it may also be a unilateral throbbing (as in cluster type headaches), which begins around one of the eyes and then spreads through the head to involve one or both sides. In severe cases, it is accompanied by anorexia, nausea and vomiting and photophobia. In addition, the extremities are cold and cyanosed, and the patient is irritable. Moreover, the scalp arteries are prominent and their amplitude of pulsation is increased. The compounds of Harris are useful in the prophylaxis and the treatment of migraine headaches and alleviating the pain associated therewith. They are administered to patients with migraine headaches in pain relieving amounts. The discussions associated with therapeutic effective amounts are applicable to the treatment and/or prophylaxis of migraine headaches (e.g., page 13).

Harris teaches that resulting mixtures of isomers can be separated into the pure isomers by methods known to one skilled in the art, e.g., by fractional distillation, crystallization and/or chromatography (see, e.g., page 11). With regards to dosages, in a preferred embodiment, the compounds utilized are administered in amounts ranging from about 1 mg to about 100 mg per kilogram of body weight per day. This dosage regimen may be adjusted by the physician to provide the optimum therapeutic response. For example, several divided doses may be administered daily or the dose may be proportionally reduced as indicated by the exigencies of the therapeutic situation. The compounds of Harris may be administered orally as tablets, troches, capsules, etc. The amount of active compound in such therapeutically useful

compositions is such that a suitable dosage will be obtained. Preferred compositions or preparations according to the present invention contains between about 10 mg and 6 g of active compound. (e.g., page 13). The principal active ingredient is compounded for convenient and effective administration in effective amounts with a suitable pharmaceutically acceptable carrier in dosage unit form. A unit dosage can, for example contain the principal active compound in amounts ranging from about 10 mg to about 6 g. Expressed in proportions, the active compound is generally present from about 1 to about 750 mg/mL of carrier. In the case of compositions containing supplementary active ingredients, the dosages are determined by reference to the usual dose and manner of administration of the said ingredients. The term patient or subject refers to a warm blooded animal, preferably mammals, such as cats, dogs, cows, pigs, mice, rats and primates, including humans. The Harris reference teaches all the active steps and population as required by claim 1, therefore, with regards to the limitation "treating a condition associated with cortical spreading depression CSD in a subject" it is deemed that it would be inherent to the method of treating headaches, migraines, chronic headaches, etc. with compounds such as (R)-2-acetamido-N-benzyl-3-methoxypropionamide as taught by Harris (See MPEP 2112). With respect to the term "prevention" please note that it does not require that the subject be afflicted with the disease. Thus, administration to a subject (e.g., Examples 1-7, pages 15-18) reads upon prevention of a condition associated with cortical spreading depression (CSD) in a subject including the conditions of instant claims 41 and 46.

Therefore the reference is deemed to anticipate the instant claims thereof.

Applicant's arguments

7. This rejection is respectfully traversed.

Harris '828 Fails to Expressly or Inherently Disclose CSD: Claim 1 Is Novel

Anticipation of a claim under 35 U.S.C. §102 requires that every limitation of the claim is disclosed, expressly or inherently, in the cited document. This is not the case here. Claim 1 recites a method for preventing or treating a condition associated with cortical spreading depression (CSD) in a subject, comprising administering to the subject, in an amount effective to suppress CSD, a compound having Formula IIb or a pharmaceutically acceptable salt thereof. Harris '828 fails to expressly disclose the method for preventing or treating a condition associated with CSD or a method including administration of an amount effective to suppress CSD. Harris '828 also fails to inherently disclose the method for preventing or treating a condition associated with CSD or a method including administration of an amount effective to suppress CSD. The Office Action at p. 6 asserts: *it is deemed that [a method of treating a condition associated with CSD] would be inherent to the method of treating headaches, migraines, chronic headaches, etc. with compound such as [harkoseride] as taught by Harris. (*emphasis added). However, CSD does not occur with all headaches, including migraines. Therefore, a method of treating a condition associated with CSD is not inherent in a method of treating a migraine. Applicant submits the following evidence to support that CSD is not inherent in migraines: CSD is just one of many possible events that can trigger a migraine headache, i.e. not all migraine sufferers have CSD. For example, Iadecola states: In 15-20% of migraine sufferers, the headache is preceded by

an 'aura'...There is increasing evidence that the aura is the result of cortical spreading depression (CSD)... See Iadecola (Feb. 2002) Nature Medicine 8(2):110-112. This means that in most migraine sufferers (75-80%), the headache is not preceded by an aura, a possible result of CSD. Furthermore, Iadecola concludes that: [i]n the majority of patients the headache is not preceded by an aura, and it is unclear whether the aura is an absolute requirement for the headache. Although it is possible that in most patients the aura is clinically silent, there is also experimental evidence that, in contrast to the findings of Bolay et al., the aura (CSD) and the headache (meningeal inflammation) are unrelated. Id., p. 111, col. 3, emphasis added; see also Bolay (Feb. 2002) Nature Medicine 8(2): 136-142, at p. 136, col. 2 ("[a]lthough a link between aura and headache was suspected, the cause for the pain remains unknown"). In other words, Iadecola recognizes that "aura (CSD)" is not necessarily present in all headaches - and may not even be related. See also Ebersberger, et al. (2001) Ann Neurol, 49:7-13, p. 11, col. 2 ("collectively, these results do not support the general hypothesis that CSD could activate the trigeminovascular system by leading to neurogenic inflammation that ultimately causes migraine headaches"). Accordingly, from the evidence submitted herein, not all subjects treated for headaches have CSD (as recited in Claim 1). So even if Harris '828 discloses treating headaches, Harris '828 does not inherently disclose treating or preventing conditions associated with CSD, or even headaches associated with CSD. The Office Action bridging p. 6-7 states: “[w]ith respect to the term "prevention" please note that it does not require that the subject be afflicted with the disease. Thus, administration to a subject (e.g., Examples 1-7, pages 15-18) reads

upon prevention of a condition associated with cortical spreading depression (CSD) in a subject including the conditions of instant claims 41 and 46." However, CSD does not occur with all headaches, including migraines. Therefore, a method of treating a condition associated with CSD is not inherent in a method of treating a migraine. Applicant submits the following evidence to support that CSD is not inherent in migraines: CSD is just one of many possible events that can trigger a migraine headache, i.e. not all migraine sufferers have CSD. For example, Iadecola states: "In 15-20% of migraine sufferers, the headache is preceded by an 'aura'...There is increasing evidence that the aura is the result of cortical spreading depression (CSD)..." See Iadecola (Feb. 2002) Nature Medicine 8(2):110-112. This means that in most migraine sufferers (75-80%), the headache is not preceded by an aura, a possible result of CSD. Furthermore, Iadecola concludes that: [i]n the majority of patients the headache is not preceded by an aura, and it is unclear whether the aura is an absolute requirement for the headache. Although it is possible that in most patients the aura is clinically silent, there is also experimental evidence that, in contrast to the findings of Bolay et al., the aura (CSD) and the headache (meningeal inflammation) are unrelated. Id., p. 111, col. 3, emphasis added; see also Bolay (Feb. 2002) Nature Medicine 8(2): 136-142, at p. 136, col. 2 ("[a]lthough a link between aura and headache was suspected, the cause for the pain remains unknown"). In other words, Iadecola recognizes that "aura (CSD)" is not necessarily present in all headaches - and may not even be related. See also Ebersberger, et al. (2001) Ann Neurol, 49:7-13, p. 11, col. 2 ("collectively, these results do not support the general hypothesis that CSD could

activate the trigeminovascular system by leading to neurogenic inflammation that ultimately causes migraine headaches"). Accordingly, from the evidence submitted herein, not all subjects treated for headaches have CSD (as recited in Claim 1). So even if Harris '828 discloses treating headaches, Harris '828 does not inherently disclose treating or preventing conditions associated with CSD, or even headaches associated with CSD. The Office Action bridging p. 6-7 states: "[w]ith respect to the term "prevention" please note that it does not require that the subject be afflicted with the disease. Thus, administration to a subject (e.g., Examples 1-7, pages 15-18) reads upon prevention of a condition associated with cortical spreading depression (CSD) in a subject including the conditions of instant claims 41 and 46." Applicant is uncertain of the conclusion drawn by this statement. However, if it is intended to mean that a method of "preventing" a condition associated with CSD is expressly or inherently found in Harris '828, this is incorrect. As set forth above, CSD is not expressly mentioned in Harris '828. Treating migraine headaches does not inherently include treating conditions associated with CSD, including migraine headaches with CSD. Accordingly, there is no disclosure of treating, much less preventing, a condition associated with CSD in Harris '828.

Furthermore, the Office Action fails to address the element of Claim 1 "administering to the subject harkoseride in an amount effective to suppress CSD". Again, Harris '828 fails to expressly disclose CSD and thus, does not disclose administering harkoseride in an amount effective to suppress CSD, or provide teaching/examples of what that amount would be. Harris '828 also fails to inherently

disclose administration in an amount effective to suppress CSD because not all migraine headaches are associated with CSD. Mere disclosure of migraines is not sufficient to anticipate Applicant's administration of harkoseride in an amount effective to suppress CSD. Therefore, Claim 1 is novel over Harris '828.

Harris '828 Fails to Expressly and Inherently Disclose CSD: Claim 44 Is Novel

Claim 44 recites a method of suppressing CSD thereby preventing a migraine. Although a distinct independent claim, Claim 44, for at least the same reasons as stated above, is novel. Since Harris '828 fails to disclose CSD, there is no express anticipation; and, since all migraine headaches do not include CSD, merely treating migraines does not necessarily include suppression of CSD, much less suppression of CSD to prevent the migraine. Accordingly, mere disclosure of treating migraines does not expressly or inherently anticipate Claim 44.

Harris '828 Fails to Expressly and Inherently Disclose Specifically Claimed Headaches: Claim 46 Is Novel

Claim 46 recites a method for preventing or treating a headache selected from the group consisting of a muscle contraction headache, a toxic headache, a cluster headache, a traction headache, or an inflammatory headache. The Office Action fails to articulate any reason why Claim 46 is anticipated by Harris '828. Since Harris '828 fails to expressly or inherently disclose treatment or prevention of any of the Markush group of headaches of claim 46, and thus claim 46 is novel over Harris ‘828.

Response to arguments

8. Applicant's arguments have been carefully considered and are deemed persuasive with respect to the methods of treatment of a condition associated with cortical spreading depression. However, with respect to the methods of prevention thereof, also claimed, the rejection is maintained since, as stated previously, prevention does not require that the subject have the condition associated with cortical spreading depression (CSD) nor does it require the subject having CSD. Therefore, administration of a compound encompassed by the instant formula IIb (such as (R)-2-acetamido-N-benzyl-3-methoxypropionamide) to a subject (e.g., Examples 1-7, pages 15-18) reads upon prevention of "a condition associated with cortical spreading depression (CSD)" in that subject including the conditions of instant claims 41 and 46. Please note that the preventive claims do not require that the subject have any specific characteristics or be afflicted by any specific diseases or CSD. With regards to the arguments drawn to "amount effective to suppress CSD", Harris (2002/0086828) at [0251] disclose that "[t]he principal active ingredient is compounded for convenient and effective administration in effective amounts with a suitable pharmaceutically acceptable carrier in dosage unit form as hereinbefore described. A unit dosage can, for example, contain the principal active compound in amounts ranging from about 10 mg to about 6 g. Expressed in proportions, the active compound is generally present from about 1 to about 750 mg/ml of carrier. In the case of compositions containing supplementary active ingredients, the dosages are determined by reference to the usual dose and manner of administration of the said ingredients.". The instant disclosure analogously teaches (see instant patent application publication) at [0104] that "[t]he principal active ingredient is compounded for

convenient and effective administration in effective amounts with a suitable pharmaceutically acceptable carrier in dosage unit form as hereinbefore described. A unit dosage form can, for example, contain the principal active compound in amounts ranging from about 10 mg to about 6 g. Expressed in proportions, the active compound is generally present in from about 1 to about 750 mg/ml of carrier. In the case of compositions containing supplementary active ingredients, the dosages are determined by reference to the usual dose and manner of administration of the said ingredients." Therefore, the limitation drawn to "amount effective to suppress CSD" is met by the references above. Thus the reference is still deemed to anticipate the instant claims above.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 1, 26-31, 42-45, 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harris (US 2002/0086828) and over Harris (US 6,884,910, cited in the IDS dated 12/4/2009).

Harris (US 2002/0086828) is the patent application corresponding to Harris (US 6,884,910). For the sake of clarity the rejection refers to Harris US 2002/0086828. However, it is noted that Harris US 6,884,910 contains parallel teachings.

Harris is relied upon as above. Further, Harris teaches that the physician will determine the dosage of the present therapeutic agents which will be most suitable and it will vary with the form of administration and the particular compound chosen, and furthermore, it will vary with the patient under treatment, the age of the patient, and the type of malady being treated. He or she will generally wish to initiate treatment at small dosages substantially less than the optimum dose of the compound and increase the dosage by small increments until the optimum effect under the circumstances is reached (e.g., page 12). With regards to dosages, in a preferred embodiment, the compounds utilized are administered in amounts ranging from about 1 mg to about 100 mg per kilogram of body weight per day. This dosage regimen may be adjusted by the physician to provide the optimum therapeutic response. For example, several divided doses may be administered daily or the dose may be proportionally reduced as indicated by the exigencies of the therapeutic situation. The compounds of Harris may be administered orally as tablets, troches, capsules, etc. The amount of active compound in such therapeutically useful compositions is such that a suitable dosage will be obtained. Preferred compositions or preparations according to the present invention contains between about 10 mg and 6 g of active compound. (e.g., page 13). The principal active ingredient is compounded for convenient and effective administration in effective amounts with a suitable pharmaceutically acceptable carrier in dosage unit form. A unit dosage can, for example contain the principal active compound in amounts ranging from about 10 mg to about 6 g. Expressed in proportions, the active compound is generally present from about 1 to about 750 mg/mL

of carrier. In the case of compositions containing supplementary active ingredients, the dosages are determined by reference to the usual dose and manner of administration of the said ingredients (e.g., pages 12-13).

Harris does not expressly teach frequencies instantly taught (e.g., daily, weekly, three doses per day, increasing doses, etc.).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to determine such frequencies and mode of administration based on the teachings of Harris. One of ordinary skill in the art at the time the invention was made would have been motivated to do so because Harris teaches that the physician will determine the dosage of the present therapeutic agents which will be most suitable and it will vary with the form of administration and the particular compound chosen, and furthermore, it will vary with the patient under treatment, the age of the patient, and the type of malady being treated. He or she will generally wish to initiate treatment at small dosages substantially less than the optimum dose of the compound and increase the dosage by small increments until the optimum effect under the circumstances is reached. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success because such adjustments were known to be within the purview of those of ordinary skill in the art.

Furthermore, with regards to the dosages, Harris does not expressly teach an absolute daily dosage. However, Harris does provide guidance in the form of therapeutic amount in an unit dosage can, for example contain the principal active compound in amounts ranging from about 10 mg to about 6 g. Also, in a preferred

embodiment, the compounds utilized are administered in amounts ranging from about 1 mg to about 100 mg per kilogram of body weight per day. For a human weighing, e.g., 100 kg, thus the daily dosage would be from 100 mg/day to 10 g/day. The dosage as taught by Harris depends on weight and all the claimed ranges are obtainable by changing the weights of the subjects. One of ordinary skill in the art at the time the invention was made would have been motivated to determine the appropriate amounts per day based on the dosage parameters taught by Harris. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success because such adjustments were known to be within the purview of those of ordinary skill in the art.

With regards to the limitation drawn to plasma concentration, please note that the Patent and Trademark Office is not equipped to conduct experimentation in order to determine whether Applicants' plasma concentration (within the claimed method) differs and, if so, to what extent, from that of the discussed reference. Therefore, with the showing of the reference, the burden of establishing non-obviousness by objective evidence is shifted to the Applicants. Further, with respect to the dosages and concentrations instantly claimed: "[g]enerally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." (MPEP 2144.05).

From the teachings of the reference, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments

11. A. Claim 1

a. Harris '828 and Harris '910 Do Not Teach or Suggest a Method To Treat or Prevent A Condition Associated With CSD

All claim limitations must be considered in judging the patentability of a claim against the prior art. See MPEP 2143.03, citing In re Wilson, 424 F.2d 1382, 165 USPQ 494 (CCPA 1970). If a reference is missing claimed features, there must be some apparent reason either in the reference or the general knowledge in the art to modify the reference to include the missing subject matter. KSR International Co. v. Teleflex Inc., 127 S.Ct. 1727, 82 USPQ 1385 (2007). As stated above, Claim 1 is directed to a method to treat or prevent a condition associated with CSD, including by administering a CSD suppressive amount of harkoseride.

The cited documents fail to disclose at least the following claim elements:

(1) CSD, and

(2) an amount of harkoseride effective to suppress CSD.

Harris '828 deals with "treating pain, in particular neuropathic pain, bipolar disease and migraine headaches." See Harris '828, at abstract. While Harris '828 does

report a method of treating pain associated, in part, with migraine headaches, Applicant's invention is directed to a method of treating or preventing conditions associated with CSD. As shown above, CSD does not occur in all migraines, and CSD is associated with a number of other conditions not remotely related to migraines. Harris '828 fails to provide disclosure, teaching or suggestion of (1) treating migraine headaches associated with CSD, (2) treating other conditions associated with CSD such as cerebrovasular diseases, intracranial hemorrhage, head injury or transient global amnesia, and (3) an effective amount of harkoseride to suppress CSD. How could Harris '828 provide guidance to an ordinary artisan regarding an amount effective to prevent or treat a condition associated with CSD, when Harris '828 does not mention CSD?

Further, the Examiner fails to provide any rational for an ordinary artisan to modify Harris '828 into a method of treating or preventing a condition associated with CSD, much less to modify Harris '828 to include administration of harkoseride in an amount effective to suppress CSD. Therefore, for at least this reason a presumption of prima facie obviousness has not been established for Claim 1 over Harris '828 or Harris '910.

b. A Method To Treat or Prevent A Condition Associated With CSD Is Unpredictable

Additionally, a method to treat or prevent a condition associated with CSD by administering an amount of harkoseride effective to suppress CSD is unpredictable. Applicant submits the following evidence of unpredictability.

"The underlying mechanism and physiological role of these blood flow related changes observed in CSD are still not fully understood." See application as filed, at p. 8, lines 9-11. Furthermore, Iadecola questions "what triggers CSD" and suggests that, at times, "the mechanisms triggering CSD remain obscure." Iadecola, at p. 111, col. 3; see also Ebersberger, at p. 11, col. 2 ("collectively, these results do not support the general hypothesis that CSD could activate the trigeminovascular system by leading to neurogenic inflammation that ultimately causes migraine headaches"). If the triggering mechanisms are obscure and CSD is not fully understood itself, how could the ordinary artisan predict that harkoseride would work to treat or prevent a condition associated with CSD, much less what would be the effective amount of harkoseride to suppress CSD. Rather, the evidence of a lack of understanding CSD, suggests that the "likely" outcome that exists in the art leads the person of ordinary skill to have an expectation of failure, rather than an expectation of success. (Applicant stresses that the standard for nonobviousness is not expectation of failure, but lack of reasonable expectation of success. A showing of expectation of failure just makes the case for nonobviousness stronger.)

In this unpredictable, complex art, Applicant was the first to identify harokseride as a compound that could prevent or treat a condition associated with CSD by administering an amount of harkoseride which suppresses CSD. Accordingly, it could not have been predicted that harkoseride, although known to be effective in reducing pain in migraine headaches generally, could actually suppress CSD and thus treat or prevent conditions associated with CSD. Therefore, for at least this additional reason a

presumption of prima facie obviousness has not been established for Claim 1 over Harris '828 or Harris '910.

B. Claim 44 and Claim 52

a. Harris '828 and Harris '910 Do Not Teach or Suggest a Method To Suppress CSD

Independent Claims 44 and 52 are directed to a method of suppressing CSD, by administering harkoseride. As set forth above, the cited documents fail to disclose the element CSD, much less teach or suggest a method for suppressing CSD. Harris '828 deals with "treating pain, in particular neuropathic pain, bipolar disease and migraine headaches." See Harris '828, at abstract. While Harris '828 is directed to pain associated, in part, with migraine headaches, Applicant's invention is directed a method to suppress CSD. As discussed above, not all migraine headaches are associated with CSD and Harris makes no disclosure, teaching, or suggestion of CSD-related migraine treatment. See MPEP 2143.03, citing In re Wilson, 424 F.2d 1382, 165 USPQ 494 (CCPA 1970) (all claim limitations must be considered in judging the patentability of a claim against the prior art); see also KSR, supra. Further, without any mention of CSD, there is no rationale for modifying Harris '828 into a method of suppressing CSD. Therefore, for at least this reason a presumption of prima facie obviousness has not been established for Claim 44 or Claim 52 over Harris '828 or Harris '910.

b. A Method To Suppress CSD Is Unpredictable

Additionally, a method to suppress CSD is also unpredictable for at least the same reasons as presented in Sec. 3(A) for Claim 1. Therefore, also for at least this

reason a presumption of prima facie obviousness has not been established for Claim 44 or Claim 52 over Harris '828 or Harris '910.

C. Dependent Claims

Claims 26-31 and 42-43 each depend directly or indirectly from Claim 1 and are, thus, non-obvious at least for all of the aforementioned reasons that make Claim 1 non-obvious.

Claim 45 depends from Claim 44, and is thus non-obvious at least for all of the aforementioned reasons that make Claim 44 non-obvious.

Withdrawal of the present rejection under 35 U.S.C. § 103(a) is respectfully requested.

Response to Arguments

12. Applicant's arguments have been carefully considered and are deemed persuasive with respect to the methods of treatment of a condition associated with cortical spreading depression. However, with respect to the methods of prevention thereof, also claimed, the rejection is maintained since, as stated previously, prevention does not require that the subject have the condition associated with cortical spreading depression (CSD) nor does it require the subject having CSD. Therefore, administration of a compound encompassed by the instant formula IIb (such as (R)-2-acetamido-N-benzyl-3-methoxypropionamide) to a subject (e.g., Examples 1-7, pages 15-18) reads upon prevention of "a condition associated with cortical spreading depression (CSD)" in that subject including the conditions of instant claims 41 and 46. Please note that the preventive claims do not require that the subject have any specific characteristics or be

afflicted by any specific diseases or CSD. With regards to the arguments drawn to "amount effective to suppress CSD", Harris (2002/0086828) at [0251] disclose that "[t]he principal active ingredient is compounded for convenient and effective administration in effective amounts with a suitable pharmaceutically acceptable carrier in dosage unit form as hereinbefore described. A unit dosage can, for example, contain the principal active compound in amounts ranging from about 10 mg to about 6 g. Expressed in proportions, the active compound is generally present from about 1 to about 750 mg/ml of carrier. In the case of compositions containing supplementary active ingredients, the dosages are determined by reference to the usual dose and manner of administration of the said ingredients.". The instant disclosure analogously teaches (see instant patent application publication) at [0104] that "[t]he principal active ingredient is compounded for convenient and effective administration in effective amounts with a suitable pharmaceutically acceptable carrier in dosage unit form as hereinbefore described. A unit dosage form can, for example, contain the principal active compound in amounts ranging from about 10 mg to about 6 g. Expressed in proportions, the active compound is generally present in from about 1 to about 750 mg/ml of carrier. In the case of compositions containing supplementary active ingredients, the dosages are determined by reference to the usual dose and manner of administration of the said ingredients." Therefore, the limitation drawn to "amount effective to suppress CSD" is met by the references above and thus, the invention as a whole is prima facie obvious over the references, especially in the absence of evidence to the contrary.

13. Claims 40, 44-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harris (US 2002/0086828) and over Harris (US 6,884,910, cited in the IDS dated 12/4/2009).

Harris (US 2002/0086828) is the patent application corresponding to Harris (US 6,884,910). For the sake of clarity the rejection refers to Harris US 2002/0086828. However, it is noted that Harris US 6,884,910 contains parallel teachings.

Harris is relied upon as above. Harris teaches that analgesics are often used to treat infrequent and mild migraines. Analgesics reduce the pain of a migraine in the case of aspirin also discourage clumping of blood platelets. However, for moderate to severe migraines, stronger medication is necessary, e.g., ergotamine, or 5-H-T1 agonists like sumatriptan (page 1). Harris also teaches that in the case of compositions containing supplementary active ingredients, the dosages are determined by reference to the usual dose and manner of administration of the said ingredients (e.g., pages 12-13).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use more than one active ingredient for the treatment of migraines or chronic headaches such as sumatriptan. One of ordinary skill in the art at the time the invention was made would have been motivated to do so because It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." (MPEP 2144.06). One of ordinary skill in the art

at the time the invention was made would have had a reasonable expectation of success since Harris Harris also teaches that in the case of compositions containing supplementary active ingredients, the dosages are determined by reference to the usual dose and manner of administration of the said ingredients (e.g., pages 12-13).

. Further, with respect to the dosages and concentrations instantly claimed: "[g]enerally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." (MPEP 2144.05).

From the teachings of the reference, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments

14. A. Claim 40

The Office Action contains no discussion of why Claim 40 is prima facie obvious in view of Harris '848 or Harris '910. Claim 40 ultimately depends from Claim 1. Therefore a presumption of prima facie obviousness has not been established for Claim 40 over Harris '848 or Harris '910 for at least the same reasons as Claim 1 (see Sec. 3(A)).

B. Claim 44

The Office Action contains no discussion of why Claim 44 is prima facie obvious in view of Harris '848 or Harris '910. Independent Claim 44 is directed to a method of suppressing CSD thereby preventing a migraine in a subject, the method comprising orally administering to the subject harkoseride. Applicant references Sec. 3(B) above which more fully articulates the reasons why a presumption of prima facie obviousness has not been established for Claim 44 over Harris '848 or Harris '910.

C. Claim 46

The Office Action provides no discussion of why Claim 46 is prima facie obvious in view of Harris '848 or Harris '910. Independent Claim 46 is directed to a method of preventing or treating a headache selected from the recited Markush group by administering an oral effective amount of harkoseride. Although Harris '828 and Harris '910 report on treatment for headaches such as migraines, Harris '828 and Harris '910 do not teach or suggest any of the types of headaches recited in Claim 46's Markush group. Therefore, a presumption of prima facie obviousness has not been established for Claim 46 over Harris '848 or Harris '910.

D. Dependent Claims 45~ 47-48

In making this second 103 rejection, the Examiner's discussion is limited to administering an agent, such as a triptan, in addition to harkoseride, and the recited dosages in the dependent claims. None of the Examiner's discussion addresses the fact that neither Harris '828 nor Harris '910 teaches or suggests (1) a method for suppressing CSD (Claim 44) nor (2) a method for preventing or treating any of the

headaches recited in Claim 46. Therefore, a presumption of prima facie obviousness over Harris '828 or Harris '910 has not been established.

Response to arguments

15. Applicant's arguments have been carefully considered and are deemed persuasive with respect to the methods of treatment of a condition associated with cortical spreading depression. However, with respect to the methods of prevention thereof, also claimed, the rejection is maintained since, as stated previously, prevention does not require that the subject have the condition associated with cortical spreading depression (CSD) nor does it require the subject having CSD. Therefore, administration of a compound encompassed by the instant formula IIb (such as (R)-2-acetamido-N-benzyl-3-methoxypropionamide) to a subject (e.g., Examples 1-7, pages 15-18) reads upon prevention of "a condition associated with cortical spreading depression (CSD)" in that subject including the conditions of instant claims 41 and 46. Please note that the preventive claims do not require that the subject have any specific characteristics or be afflicted by any specific diseases or CSD. With regards to the arguments drawn to "amount effective to suppress CSD", Harris (2002/0086828) at [0251] disclose that "[t]he principal active ingredient is compounded for convenient and effective administration in effective amounts with a suitable pharmaceutically acceptable carrier in dosage unit form as hereinbefore described. A unit dosage can, for example, contain the principal active compound in amounts ranging from about 10 mg to about 6 g. Expressed in proportions, the active compound is generally present from about 1 to about 750 mg/ml of carrier. In the case of compositions containing supplementary active ingredients, the

dosages are determined by reference to the usual dose and manner of administration of the said ingredients.". The instant disclosure analogously teaches (see instant patent application publication) at [0104] that "[t]he principal active ingredient is compounded for convenient and effective administration in effective amounts with a suitable pharmaceutically acceptable carrier in dosage unit form as hereinbefore described. A unit dosage form can, for example, contain the principal active compound in amounts ranging from about 10 mg to about 6 g. Expressed in proportions, the active compound is generally present in from about 1 to about 750 mg/ml of carrier. In the case of compositions containing supplementary active ingredients, the dosages are determined by reference to the usual dose and manner of administration of the said ingredients." Therefore, the limitation drawn to "amount effective to suppress CSD" is met by the references above and thus, the invention as a whole is prima facie obvious over the references, especially in the absence of evidence to the contrary.

16. Claims 1-4, 14, 16-18, 20, 24, 32-36, 41, 44, 46-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harris (US 2002/0086828) in view of Iadecola (Nature Medicine, February 2002, cited in the IDS dated 7/9/2010) and over Harris (US 6,884,910, cited in the IDS dated 12/4/2009) in view of Iadecola (Nature Medicine, February 2002, cited in the IDS dated February 2002, cited in the IDS dated 7/9/2010).

Harris (US 2002/0086828) is the patent application corresponding to Harris (US 6,884,910). For the sake of clarity the rejection refers to Harris US 2002/0086828. However, it is noted that Harris US 6,884,910 contains parallel teachings.

Harris '828 discloses a method of treating chronic headaches, migraines and acute migraines with the compound (R)-2-acetamido-N-benzyl-3-methoxypropionamide and also with other compounds embraced by the genus of Formula II, i.e., O-methyl-N-acetyl-D-serine-p-fluorobenzylamide, O-methyl-N-acetyl-D-serine-p-fluorobenzyl amide, etc. (e.g., pages 7-8).

Harris teaches that a migraine headache is defined as a periodically occurring (i.e., chronic) vascular headache characterized by pain in the head (usually unilateral), nausea and vomiting, photophobia, phenophobia, vertigo and general weakness. Migraine is the most common type of vascular headache and affects as many as 15% of the world's population. Of the different types of migraines, classical migraine and common migraine are the two most prevalent. The major difference between the two types of migraines is that classical migraines are preceded by the appearance of neurological symptoms before an attack whereas common migraines are not preceded by such symptoms. Migraine is caused by intermittent brain dysfunction. However, the precise pathophysiological mechanism involved are not understood. The head-pain is believed to involve blood vessel dilation and a reduction of the brain's pain relieving chemicals. Harris teaches that analgesics are often used to treat infrequent and mild migraines. Analgesics reduce the pain of a migraine in the case of aspirin also discourage clumping of blood platelets. However, for moderate to severe migraines, stronger medication is necessary, e.g., ergotamine, or 5-H-T1 agonists like sumatriptan (page 1). Harris goes on to teach that alternatives for treatment are necessary given the inadequacy of current therapy in completely alleviating the pain from those who

have moderate to heavy (i.e., acute) migraine headaches (page 1).Harris discloses that a migraine headache is a paroxysmal disorder characterized by recurrent attacks of headaches, which may be associated with visual (as in cluster type headaches) or GI disturbances, the pain is usually generalized, but it may also be a unilateral throbbing (as in cluster type headaches), which begins around one of the eyes and then spreads through the head to involve one or both sides. In severe cases, it is accompanied by anorexia, nausea and vomiting and photophobia. In addition, the extremities are cold and cyanosed, and the patient is irritable. Moreover, the scalp arteries are prominent and their amplitude of pulsation is increased. The compounds of Harris are useful in the prophylaxis and the treatment of migraine headaches and alleviating the pain associated therewith. They are administered to patients with migraine headaches in pain relieving amounts. The discussions associated with therapeutic effective amounts are applicable to the treatment and/or prophylaxis of migraine headaches (e.g., page 13).

Harris teaches that resulting mixtures of isomers can be separated into the pure isomers by methods known to one skilled in the art, e.g., by fractional distillation, crystallization and/or chromatography (see, e.g., page 11). With regards to dosages, in a preferred embodiment, the compounds utilized are administered in amounts ranging from about 1 mg to about 100 mg per kilogram of body weight per day. This dosage regimen may be adjusted by the physician to provide the optimum therapeutic response. For example, several divided doses may be administered daily or the dose may be proportionally reduced as indicated by the exigencies of the therapeutic

situation. The compounds of Harris may be administered orally as tablets, troches, capsules, etc. The amount of active compound in such therapeutically useful compositions is such that a suitable dosage will be obtained. Preferred compositions or preparations according to the present invention contains between about 10 mg and 6 g of active compound. (e.g., page 13). The principal active ingredient is compounded for convenient and effective administration in effective amounts with a suitable pharmaceutically acceptable carrier in dosage unit form. A unit dosage can, for example contain the principal active compound in amounts ranging from about 10 mg to about 6 g. Expressed in proportions, the active compound is generally present from about 1 to about 750 mg/mL of carrier. In the case of compositions containing supplementary active ingredients, the dosages are determined by reference to the usual dose and manner of administration of the said ingredients. The term patient or subject refers to a warm blooded animal, preferably mammals, such as cats, dogs, cows, pigs, mice, rats and primates, including humans.

Harris et al. do not expressly teach treating a migraine that has a CSD component. However, it was well known in the art at the time the invention was made that in 15-20% of migraine sufferers, the headache is preceded by an 'aura' which typically consist of flashing lights or shiny angular shapes that slowly drift across the visual field, and last for about 20-30 minutes. Toward the end of the aura, the flashing lights become transient spots as taught by Iadecola. Iadecola further teaches that there is increasing evidence that the aura is the result of cortical spreading depression (CSD), a wave of neuronal depolarization that spreads across the cerebral cortex. Iadecola

further indicates that evidence seems to point out that CSD activates trigeminal afferents that, through central and peripheral reflex mechanisms, cause inflammatory changes in the pain-sensitive meninges to generate the headache and thus provide a link between CSD and the meningeal alterations underlying the headache (page 110).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have used the method of treating migraines of Harris in the 15-20% of migraine sufferers that had auras due to CSD as taught by Iadecola or having acute migraines. One of ordinary skill in the art at the time the invention was made would have been motivated to do so because Harris et al. teach a method for the prophylaxis or treatment of migraine headaches in a subject, comprising administering to said patient a headache relieving effective amount of a compound encompassed by the instantly claimed formula IIb. Furthermore, with regards to the limitation "amount effective to suppress CSD", Harris (2002/0086828) at [0251] disclose that "[t]he principal active ingredient is compounded for convenient and effective administration in effective amounts with a suitable pharmaceutically acceptable carrier in dosage unit form as hereinbefore described. A unit dosage can, for example, contain the principal active compound in amounts ranging from about 10 mg to about 6 g. Expressed in proportions, the active compound is generally present from about 1 to about 750 mg/ml of carrier. In the case of compositions containing supplementary active ingredients, the dosages are determined by reference to the usual dose and manner of administration of the said ingredients.". The instant disclosure analogously teaches (see instant patent application publication) at [0104] that "[t]he principal active ingredient is compounded for

convenient and effective administration in effective amounts with a suitable pharmaceutically acceptable carrier in dosage unit form as hereinbefore described. A unit dosage form can, for example, contain the principal active compound in amounts ranging from about 10 mg to about 6 g. Expressed in proportions, the active compound is generally present in from about 1 to about 750 mg/ml of carrier. In the case of compositions containing supplementary active ingredients, the dosages are determined by reference to the usual dose and manner of administration of the said ingredients." Thus the amounts are overlapping and therefore the amount administered in Harris et al. to treat/prevent migraine reads upon an effective amount to suppress CSD. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success since Harris et al. are drawn to preventing and treating any migraine, including those associated with CSD and/or acute migraines since Harris is not limited to preventing/treating a certain the type of migraines.

Thus, the invention as a whole is prima facie obvious over the references, especially in the absence of evidence to the contrary.

17. Claims 1, 26-31, 42-45, 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harris (US 2002/0086828) in view of Iadecola (Nature Medicine, February 2002, cited in the IDS dated 7/9/2010) and over Harris (US 6,884,910, cited in the IDS dated 12/4/2009) in view of in view of Iadecola (Nature Medicine, February 2002, cited in the IDS dated 7/9/2010).

Harris (US 2002/0086828) is the patent application corresponding to Harris (US 6,884,910). For the sake of clarity the rejection refers to Harris US 2002/0086828. However, it is noted that Harris US 6,884,910 contains parallel teachings.

Harris and Iadecola are relied upon as above. Further, Harris teaches that the physician will determine the dosage of the present therapeutic agents which will be most suitable and it will vary with the form of administration and the particular compound chosen, and furthermore, it will vary with the patient under treatment, the age of the patient, and the type of malady being treated. He or she will generally wish to initiate treatment at small dosages substantially less than the optimum dose of the compound and increase the dosage by small increments until the optimum effect under the circumstances is reached (e.g., page 12). With regards to dosages, in a preferred embodiment, the compounds utilized are administered in amounts ranging from about 1 mg to about 100 mg per kilogram of body weight per day. This dosage regimen may be adjusted by the physician to provide the optimum therapeutic response. For example, several divided doses may be administered daily or the dose may be proportionally reduced as indicated by the exigencies of the therapeutic situation. The compounds of Harris may be administered orally as tablets, troches, capsules, etc. The amount of active compound in such therapeutically useful compositions is such that a suitable dosage will be obtained. Preferred compositions or preparations according to the present invention contains between about 10 mg and 6 g of active compound. (e.g., page 13). The principal active ingredient is compounded for convenient and effective administration in effective amounts with a suitable pharmaceutically acceptable carrier

in dosage unit form. A unit dosage can, for example contain the principal active compound in amounts ranging from about 10 mg to about 6 g. Expressed in proportions, the active compound is generally present from about 1 to about 750 mg/mL of carrier. In the case of compositions containing supplementary active ingredients, the dosages are determined by reference to the usual dose and manner of administration of the said ingredients (e.g., pages 12-13).

Harris does not expressly teach frequencies instantly taught (e.g., daily, weekly, three doses per day, increasing doses, etc.).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to determine such frequencies and mode of administration based on the teachings of Harris. One of ordinary skill in the art at the time the invention was made would have been motivated to do so because Harris teaches that the physician will determine the dosage of the present therapeutic agents which will be most suitable and it will vary with the form of administration and the particular compound chosen, and furthermore, it will vary with the patient under treatment, the age of the patient, and the type of malady being treated. He or she will generally wish to initiate treatment at small dosages substantially less than the optimum dose of the compound and increase the dosage by small increments until the optimum effect under the circumstances is reached. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success because such adjustments were known to be within the purview of those of ordinary skill in the art.

Furthermore, with regards to the dosages, Harris does not expressly teach an absolute daily dosage. However, Harris does provide guidance in the form of therapeutic amount in an unit dosage can, for example contain the principal active compound in amounts ranging from about 10 mg to about 6 g. Also, in a preferred embodiment, the compounds utilized are administered in amounts ranging from about 1 mg to about 100 mg per kilogram of body weight per day. For a human weighing, e.g., 100 kg, thus the daily dosage would be from 100 mg/day to 10 g/day. The dosage as taught by Harris depends on weight and all the claimed ranges are obtainable by changing the weights of the subjects. One of ordinary skill in the art at the time the invention was made would have been motivated to determine the appropriate amounts per day based on the dosage parameters taught by Harris. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success because such adjustments were known to be within the purview of those of ordinary skill in the art.

With regards to the limitation drawn to plasma concentration, please note that the Patent and Trademark Office is not equipped to conduct experimentation in order to determine whether Applicants' plasma concentration (within the claimed method) differs and, if so, to what extent, from that of the discussed reference. Therefore, with the showing of the reference, the burden of establishing non-obviousness by objective evidence is shifted to the Applicants. Further, with respect to the dosages and concentrations instantly claimed: "[g]enerally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the

prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." (MPEP 2144.05).

From the teachings of the reference, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

18. Claims 40, 44-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harris (US 2002/0086828) in view of Iadecola (Nature Medicine, February 2002, cited in the IDS dated 7/9/2010) and over Harris (US 6,884,910, cited in the IDS dated 12/4/2009) in view of Iadecola (Nature Medicine, February 2002, cited in the IDS dated 7/9/2010).

Harris (US 2002/0086828) is the patent application corresponding to Harris (US 6,884,910). For the sake of clarity the rejection refers to Harris US 2002/0086828. However, it is noted that Harris US 6,884,910 contains parallel teachings.

Harris and Iadecola relied upon as above. Harris teaches that analgesics are often used to treat infrequent and mild migraines. Analgesics reduce the pain of a migraine in the case of aspirin also discourage clumping of blood platelets. However, for moderate to severe migraines, stronger medication is necessary, e.g., ergotamine, or 5-H-T1 agonists like sumatriptan (page 1). Harris also teaches that in the case of

compositions containing supplementary active ingredients, the dosages are determined by reference to the usual dose and manner of administration of the said ingredients (e.g., pages 12-13).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use more than one active ingredient for the treatment of migraines or chronic headaches such as sumatriptan. One of ordinary skill in the art at the time the invention was made would have been motivated to do so because It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." (MPEP 2144.06). One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success since Harris Harris also teaches that in the case of compositions containing supplementary active ingredients, the dosages are determined by reference to the usual dose and manner of administration of the said ingredients (e.g., pages 12-13).

. Further, with respect to the dosages and concentrations instantly claimed: "[g]enerally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." (MPEP 2144.05).

From the teachings of the reference, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

19. No claim is allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARCELA M. CORDERO GARCIA whose telephone number is (571)272-2939. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia J. Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a

USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Marcela M Cordero Garcia/
Examiner, Art Unit 1654

MMCG 02/2010